

A time scales approach to coinfection by opportunistic diseases.

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Abstract

Traditional biomedical approaches treat diseases in isolation, but the importance of synergistic disease interactions is now recognized. As a first step we present and analyze a simple coinfection model for two diseases affecting simultaneously a population. The host population is affected by the *primary disease*, a long-term infection whose dynamics is described by a SIS model with demography, which facilitates individuals acquiring a second disease, *secondary (or opportunistic) disease*. The secondary disease is instead a short-term infection affecting only the primary-infected individuals. Its dynamics is also represented by a SIS model with no demography. To distinguish between short and long-term infection the complete model is written as a two time scales system. The primary disease acts at the slow time scale while the secondary disease does at the fast one, allowing a dimension reduction of the system and making its analysis tractable. We show that an opportunistic disease outbreak might change drastically the outcome of the primary epidemic process, although it does among the outcomes allowed by the primary disease. We have found situations in which either acting on the

opportunistic disease transmission or recovery rates or controlling the susceptible and infected population size allow to eradicate/promote disease endemicity.

1 Introduction.

Coinfection is the simultaneous infection of a host by multiple pathogen species. The global incidence of coinfection among humans is huge [12] and supposed to be more common than single infection. The interactions between pathogen species within their host can have either positive or negative effects on each other. The net effect of coinfection on human health is thought to be negative [15].

The case of positive parasite interactions falls into the concept of *syndemic*: aggregation of two or more diseases in a population in which there is some level of positive biological interaction that exacerbates the negative health effects of any or all of the diseases [23]. From the point of view of prevention and treatment of disease it is the opposite case that is important, sometimes called *counter syndemic*: disease interactions that yield a lower whole effect than the sum effects of the individual diseases involved. An example of counter syndemic is that of human immunodeficiency virus (HIV) transiently suppressed during acute measles infections. A broadly extended syndemic involves tuberculosis (TB) and HIV [20]. The World Health Organization [27] reports that people living with HIV are around 30 times more likely to develop TB than persons without HIV and also that TB is the most common illness occurring among people living with HIV. Other syndemics involving infectious diseases have been described in the literature: HIV and malaria syndemic [1]; the helminthic infections, malaria and HIV/AIDS syndemic [16]; the pertussis, influenza, tuberculosis syndemic [17]; and the HIV and sexually transmitted disease (STD) syndemic [13].

In this work we deal with a particular, but very common, type of coinfection. We consider the interactions of two diseases, the first one of the type called *primary disease* and the second one of the *opportunistic disease* type. Only relatively few pathogen species cause disease in otherwise healthy individuals [5]. Those few are called primary pathogens. The diseases that they cause, primary diseases, are the result of their only activity within a healthy host. An opportunistic disease, on the other hand, is characterized [26] as a serious, usually progressive infection by a micro-organism that has limited (or no) pathogenic capacity under ordinary circumstances, but which has been able to cause serious disease as a result of the predisposing effect of another disease or of its treatment.

The importance of opportunistic diseases for public health [15, 19, 28] is underrepresented in the mathematical modelling literature. A reason for that is that models of

coinfection usually result in large dimensional systems which are difficult to be studied analytically. The main aim of this work is to settle a model describing the interaction between both, the primary and the secondary diseases. The model that we present in this work tries to capture the basic features of a coinfection model using for it the least possible number of variables. The dynamics of the primary disease is represented by means of a SIS model. All individuals affected by the primary infection are assumed to be susceptible of being infected by the opportunistic disease. As the dynamics of the opportunistic disease is also described in terms of a SIS model we only distinguish three types of individuals in the population: individuals with no infection, *susceptible*, individuals infected by the primary disease but not by the opportunistic disease, *primary infected*, and individuals infected by both diseases, *coinfected*.

Specifically, we want to know whether or not the coinfection by a secondary disease produces epidemiological scenarios not allowed by the primary disease submodel. In the latter case, it is of interest to assess if coinfection has any influence on the actual outcome of the model, even if it is only among those allowed by the primary disease submodel. On the other hand, and in any case, we look for identifying mechanisms to modulate the epidemiological outcome.

A primary disease enabling secondary infections has typically a long illness period. It must produce a persistent alteration of the immune response which weakens the body's ability to clear secondary diseases. On the other hand, a compromised immune system presents an opportunity that a secondary pathogen must rapidly take advantage of. As a simplified approximation of the general case we suppose that the primary disease is a long-term infection that evolves slowly compared to the opportunistic disease which has a rapid evolution and, thus, can be considered a short-term infection. This difference in the acting speed of both infections is reflected in our model in two different issues. Firstly, we assume that demography has an impact in the primary disease, due to its slow evolution, whereas it is negligible for the opportunistic disease which evolves in a short period of time. Secondly, the system of differential equations, in terms of which we express our model, possesses two time scales: the slow one encompassing the demography and the primary disease evolution and the fast one associated to the opportunistic disease evolution.

The inclusion of two time scales in the system has the advantage of allowing its reduction. The asymptotic behavior of the solutions of the initial three dimensional system can be studied through a planar system. The reduction of the system is undertaken with the help of aggregation methods [3, 4, 21]. The general aim of these methods is studying the relationships between a large class of complex systems, in which many variables are involved, and their corresponding reduced or aggregated systems, governed

by a few global variables. The idea behind the reduction of the system in our model is considering the evolution of the secondary infection as instantaneous in relation to that of the primary one. Obviously this is but an approximation which, on the other hand, can be precisely treated with the help of the aggregation method. The steady state rapidly, almost instantaneously, reached by the opportunistic disease serves to merging in one single variable those variables corresponding to primary infected and coinfecting individuals. The result is a SIS type model where the effect of the opportunistic disease is reflected in its parameters.

The model is presented in Section 2. In this section the reduction of the system is also included. Section 3 is devoted to the analysis of the reduced system. This analysis allows a discussion of the permanence of the population as well as of the influence of the final size of the opportunistic disease on the outcome of the primary epidemic. This discussion is the content of section 4.

2 The model

We build up in this section a model of coinfection that describes the interaction between two diseases, one of primary type whereas the second one is of opportunistic type. Only the individuals infected by the primary disease are susceptible of being infected by the opportunistic disease. Moreover, the interaction of both diseases occurs at different time scales, being the evolution of the opportunistic disease much faster than that of the primary one. The model is written in terms of a slow-fast ordinary differential equations model. After building the slow-fast model, the separation of time scales allows us to apply approximate aggregation techniques [3, 4] to get a smaller dimensional system. For the convenience of readers non familiar with it, the reduction procedure is sketched in subsection 2.4. The section finishes describing which kind of information about the slow-fast system can be retrieved from the reduced system.

2.1 The primary disease sub-model

The primary disease dynamics is described by a SIS model with demographic effects. In a SIS model individuals are divided into susceptible (S) and infected (I). The latter return to the susceptible class on recovery because the disease confers no immunity against reinfection [8]. It is appropriate for most diseases transmitted by bacterial or helminth agents, and most sexually transmitted diseases. Concerning transmission, there are two extreme traditional forms [18] the density-dependent transmission (DDT) and the frequency-dependent transmission (FDT). In DDT the rate of contact between

susceptible and infected individuals increases with host density while in FDT this rate of contact is independent of host density. The fact that the primary disease acts together with demography at the same time scale leads us to assume it does with density-dependent transmission. On the other hand, in the case of the opportunistic disease which turns out to evolve at a faster time scale we consider that it does with frequency-dependent transmission [22, 7].

We denote by γ the recovery rate and by β the constant transmission rate. The parameter μ describes the additional disease-induced mortality.

We consider demographic effects with only horizontal transmission of the disease. In many mathematical models, from a demographic point of view, the differences between susceptible and infected individuals are reduced to an additional disease-related death rate or disease induced reduction in fecundity [9]. However, there are experimental evidences of the influence of disease on host competitive abilities [6] which have already been introduced in eco-epidemiological models [24]. We adopt this last approach. The intrinsic per-capita fertility rate of uninfected individuals is given by r . The reduction on intrinsic per-capita fertility rate of infected individuals is represented by the parameter $a \in (0, 1)$. The natural death rate is denoted m . The effects of intra-specific competition reducing population growth are introduced in the model by means of parameters c_{SS} , c_{SI} , c_{IS} and c_{II} . To be precise, the parameters c_{SS} and c_{II} represent intra-class competition between susceptible and infected individuals, respectively, whereas the parameters c_{SI} and c_{IS} introduce the inter-class impact of infected on susceptible individuals and of susceptible on infected individuals, respectively.

The primary disease submodel is given by the equations

$$\begin{cases} \frac{dS}{dt} = & rS + arI - mS & - (c_{SS}S + c_{SI}I)S & - \beta SI + \gamma I, \\ \frac{dI}{dt} = & \underbrace{-mI}_{\text{density independent growth}} & \underbrace{-(c_{IS}S + c_{II}I)I}_{\text{competition}} & \underbrace{+\beta SI - \gamma I - \mu I}_{\text{transmission, recovery and disease mortality}} \end{cases} \quad (1)$$

As mentioned in the introduction, to our knowledge, the primary disease submodel (1) has not been previously analyzed. However, we postpone its analysis until section 3, once we have described the full model and the aforementioned reduction process.

2.2 The opportunistic disease sub-model

The opportunistic disease spreads only through the individuals infected by the primary disease. We consider that the opportunistic disease dynamics is also described by a SIS model. Individuals infected by the primary disease are further classified into those not

infected by the opportunistic disease (U), primary infected, and those infected by both diseases (V), coinfectd.

The fast evolution of the opportunistic disease, compared to primary disease and demography, suggests not including demographic effects and choosing the frequency-dependent transmission form. Let λ and δ be, respectively, the constant transmission and recovery rates.

The opportunistic disease submodel is represented by the equations

$$\begin{cases} \frac{dU}{d\tau} = -\lambda \frac{UV}{U+V} + \delta V, \\ \frac{dV}{d\tau} = \lambda \frac{UV}{U+V} - \delta V. \end{cases} \quad (2)$$

We use τ to denote the time variable for the fast time scale. It is related to variable time t in system (1) as $t = \varepsilon\tau$ where ε is a small positive constant representing the ratio between time scales.

2.3 The full two time-scales model

Finally, we construct the model encompassing both diseases. It has the form of a system with three state variables: susceptible S , primary infected U and coinfectd V individuals. It is a system with two time scales that is expressed in terms of the fast time variable τ . The terms associated to the slow time scale, demography and primary disease dynamics, appear multiplied by ε in (3). The fast part of system (3), the opportunistic disease dynamics, coincides with system (2).

In the slow part of system (3) we have to define different rates for primary infected and coinfectd individuals. We denote β_U and β_V the constant primary disease transmission rates due to primary infected and coinfectd individuals, respectively. We assume that there is no direct connection between the susceptible and coinfectd stages. A susceptible individual must first acquire the primary disease and later be infected by the opportunistic one. On the other hand, a coinfectd individual must first recover from the opportunistic disease and then, being just primary infected, can also recover from the primary one. The primary disease recovery rate is still denoted γ . Parameters μ_U and μ_V describe the additional primary disease-induced mortality in primary infected and coinfectd individuals, respectively.

Concerning the part of demography, we keep the same intrinsic per-capita fertility rate of uninfected individuals r and the natural death rate of the population m as in system (1). We include different coefficients of reduction on intrinsic per-capita fertility rate for primary infected and coinfectd individuals: a_U and a_V . We assume

them to verify $0 < a_V < a_U < 1$ supposing that coinfecting individuals participate in reproduction though at a smaller rate. To distinguish the effects of intraspecific competition among the three stages we need to introduce nine parameters c_{SS} , c_{SU} , c_{SV} , c_{US} , c_{UU} , c_{UV} , c_{VS} , c_{VU} and c_{VV} . They represent the competition, either intra-class or inter-class, between the two stages in each of the nine different interaction pairs.

The complete two time scales system reads as follows

$$\begin{cases} \frac{dS}{d\tau} = \varepsilon \left[rS + a_U rU + a_V rV - mS - (c_{SS}S + c_{SU}U + c_{SV}V)S - \beta_U SU - \beta_V SV + \gamma U \right], \\ \frac{dU}{d\tau} = -\frac{\lambda UV}{U+V} + \delta V \\ \quad + \varepsilon \left[-mU - (c_{US}S + c_{UU}U + c_{UV}V)U + \beta_U SU + \beta_V SV - \gamma U - \mu_U U \right], \\ \frac{dV}{d\tau} = \frac{\lambda UV}{U+V} - \delta V + \varepsilon \left[-mV - (c_{VS}S + c_{VU}U + c_{VV}V)V - \mu_V V \right]. \end{cases} \quad (3)$$

2.4 Reduction of the model

In this section we take advantage of the two time scales to reduce the dimension of the complete system (3). In the next section, as a consequence of this reduction, we perform the analysis of the model by means of a planar system. The reduction follows the technique called *approximate aggregation method* [3, 4]. The first step is writing the system in the so-called slow-fast form. This is easily done in system (3) using the change of variables $(S, U, V) \mapsto (S, I, V)$ where $I = U + V$ represents all the infected individual, both primary infected and coinfecting.

$$\begin{cases} \frac{dS}{d\tau} = \varepsilon \left[rS + a_U r(I - V) + a_V rV - mS - (c_{SS}S + c_{SU}(I - V) + c_{SV}V)S \right. \\ \quad \left. - \beta_U S(I - V) - \beta_V SV + \gamma(I - V) \right], \\ \frac{dI}{d\tau} = \varepsilon \left[-mI - (c_{US}S + c_{UU}(I - V) + c_{UV}V)(I - V) + \beta_U S(I - V) + \beta_V SV \right. \\ \quad \left. - \gamma(I - V) - \mu_U(I - V) - (c_{VS}S + c_{VU}(I - V) + c_{VV}V)V - \mu_V V \right], \\ \frac{dV}{d\tau} = \frac{\lambda(I - V)V}{I} - \delta V + \varepsilon \left[-mV - (c_{VS}S + c_{VU}(I - V) + c_{VV}V)V - \mu_V V \right]. \end{cases} \quad (4)$$

The key point of the new form of system (3) is making visible that variables S and I are slow (the right hand side terms of their equations have ε as a factor) in the sense that

they almost do not change at the fast time scale. The fast dynamics is concentrated in the first terms without ε in the equation for V . The approximation that the aggregation method proposes consist in separating both dynamics. Firstly, the non slow variables are calculated in terms of the slow ones by assuming that they are the equilibria (called *fast equilibria*) determining the long term behaviour of the fast dynamics. Secondly, these obtained values of the non slow variables are substituted into the equations of the slow ones yielding a reduced system for the latter. In this reduced or aggregated system the fast dynamics is summarized in its parameters. In the particular case of system (4), the only non slow variable is V and the fast dynamics reduces to the equation

$$\frac{dV}{d\tau} = \frac{\lambda(I - V)V}{I} - \delta V. \quad (5)$$

Assuming the slow variable I to be constant, the analysis of equation (5) gives that for positive values of $V(0)$

$$\lim_{\tau \rightarrow \infty} V(\tau) = \nu^* I = \begin{cases} 0 & \text{if } \delta \geq \lambda \\ (1 - \delta/\lambda)I & \text{if } \delta < \lambda \end{cases} \quad (6)$$

which corresponds to the results of a classical SIS model without demography and frequency-dependent transmission [8]. If the recovery rate is larger than the transmission rate, the disease disappears since the number of coinfecting individuals tends rapidly to zero. On the other hand, if the recovery rate is smaller than the transmission rate, the disease becomes endemic with a stable fraction $\nu^* = 1 - \delta/\lambda$ of the infected population I remaining coinfecting.

The fast equilibria $V = \nu^* I$ found in (5) are the values to be substituted into the equations for the slow variables S and I to obtain the following reduced system

$$\begin{cases} \frac{dS}{dt} = rS + \bar{a}rI - mS - (c_{SS}S + \bar{c}_{SI}I)S - \bar{\beta}SI + \bar{\gamma}I, \\ \frac{dI}{dt} = -mI - (\bar{c}_{IS}S + \bar{c}_{II}I)I + \bar{\beta}SI - \bar{\gamma}I - \bar{\mu}I, \end{cases} \quad (7)$$

which has the same form as the primary disease sub-model (1). In its parameters the effect of fast dynamics, the opportunistic disease, is implicit through ν^* :

$$\begin{aligned} \bar{a} &= (1 - \nu^*)a_U + \nu^*a_V, \quad \bar{c}_{SI} = (1 - \nu^*)c_{SU} + \nu^*c_{SV}, \quad \bar{c}_{IS} = (1 - \nu^*)c_{US} + \nu^*c_{VS}, \\ \bar{c}_{II} &= (1 - \nu^*)^2 c_{UU} + (1 - \nu^*)\nu^* c_{UV} + \nu^*(1 - \nu^*)c_{VU} + (\nu^*)^2 c_{VV}, \\ \bar{\beta} &= (1 - \nu^*)\beta_U + \nu^*\beta_V, \quad \bar{\gamma} = (1 - \nu^*)\gamma, \quad \bar{\mu} = (1 - \nu^*)\mu_U + \nu^*\mu_V \end{aligned} \quad (8)$$

The reduced system (7) is useful to analyze the asymptotic behaviour of the solutions of the complete system (3) [3, 4]. In particular, the existence of a hyperbolic asymptotically stable equilibria (S^*, I^*) of system (7) ensures the existence, for ε small enough, of an equilibria of system (3) with the same characteristics and a form very close to $(S^*, (1 - \nu^*)I^*, \nu^*I^*)$. In the next section we carry out the analysis of the stability of equilibria of system (7) obtaining thus the corresponding results for the complete model (3).

Note that the reduced system (7) and the primary disease submodel (1) are the same, the only difference being the values of the respective coefficients. Indeed, when $\delta > \lambda$ the opportunistic disease cannot invade the population and, in this case, the coefficients (8) of systems (7) and (1) are exactly the same.

3 Analysis of the reduced system

We proceed in this section to analyze the reduced system (7).

We first note that $E_0^* = (0, 0)$ is an equilibrium point, the positive S semi-axis, $\{(S, 0) : S > 0\}$, is invariant and on the positive I semi-axis, $\{(0, I) : I > 0\}$, the vector field associated to system (7) points to the interior of the positive quadrant. We then have that the closed positive quadrant $\mathbb{R}_+^2 = \{(S, I) : S \geq 0, I \geq 0\}$ is positively invariant.

In the next result we prove that, as expected, if the susceptible fertility rate r is not strictly larger than the natural death rate m the population gets extinct.

Proposition 1 *If $r \leq m$ then any solution $(S(t), I(t))$ of system (7) with non-negative initial conditions $(S(0), I(0))$ tends to E_0^* .*

Proof: Let us call $W = S + I$. Summing up both equations in system (7) and now choosing $c = \min\{c_{SS}, \bar{c}_{SI}, \bar{c}_{IS}, \bar{c}_{II}\}$ we have $\frac{dW}{dt} \leq -cW^2$ that, by integration, yields

$$0 \leq W(t) \leq \frac{W(0)}{1 + W(0)ct} \xrightarrow{t \rightarrow \infty} 0$$

since \mathbb{R}_+^2 is positively invariant. ■

Henceforth we assume that $r > m$. This assumption prevents the population from extinction. The linearization of system (7) at the equilibrium E_0^* has the matrix

$$\begin{pmatrix} r - m & \bar{a}r + \bar{\gamma} \\ 0 & -(m + \bar{\gamma} + \bar{\mu}) \end{pmatrix}$$

with one positive and one negative eigenvalues. The unstable manifold of E_0^* , associated to $r - m$, is included in the S axis, while the stable manifold, associated to $-(m + \bar{\gamma} + \bar{\mu})$, is tangent at $\mathbf{0}$ to the eigenvector $(\bar{a}r + \bar{\gamma}, -(r + \bar{\gamma} + \bar{\mu}))$ and lies completely outside the interior of the positive quadrant.

Assuming $r > m$ the only non-negative solution tending to $\mathbf{0}$ is E_0^* itself. We prove next that all non-negative solutions are forward bounded.

Proposition 2 *Let $r > m$. If $(S(t), I(t))$ is any solution of system (7) with non-negative initial conditions $(S(0), I(0))$ then it is bounded on $[0, \infty)$.*

Proof: Calling $W = S + I$ and letting $c = \min\{c_{SS}, \bar{c}_{SI}, \bar{c}_{IS}, \bar{c}_{II}\}$ we have

$$\frac{dW}{dt} + (r - m)W \leq 2(r - m)W - cW^2$$

Function $g(W) = 2(r - m)W - cW^2$ attains its maximum on $[0, \infty)$ at $W = (r - m)/c$, so that

$$\frac{dW}{dt} + (r - m)W \leq \frac{(r - m)^2}{c}.$$

Multiplying both sides of the previous inequality by $e^{(r-m)t}$ and rearranging terms yields

$$\frac{d}{dt}(e^{(r-m)t}W) \leq e^{(r-m)t} \frac{(r - m)^2}{c},$$

that implies, integrating on $[0, t]$,

$$e^{(r-m)t}W(t) - W(0) \leq \frac{(r - m)^2}{c(r - m)}(e^{(r-m)t} - 1).$$

Rearranging terms in the previous expression leads to

$$W(t) \leq W(0)e^{-(r-m)t} + \frac{r - m}{c}(1 - e^{-(r-m)t})$$

and, finally, we have that $W(t) \leq \max\{W(0), (r - m)/c\}$ for every $t \in [0, \infty)$. ■

In addition to the trivial equilibrium E_0^* , the system (7) possesses a disease-free equilibrium $E_1^* = (S_1^*, 0)$, where

$$S_1^* = \frac{r - m}{c_{SS}}$$

that represents the stable size of the population in case of no infection. The growth of the population in the absence of infections is logistic and S_1^* represents its carrying capacity.

Proposition 3 *Let $r > m$. The equilibrium point $E_1^* = (S_1^*, 0)$ of system (7) verifies:*

1. *If $S_1^*(\bar{\beta} - \bar{c}_{IS}) > m + \bar{\gamma} + \bar{\mu}$ then E_1^* is a saddle point of which stable manifold coincides with the positive S semi-axis.*
2. *If $S_1^*(\bar{\beta} - \bar{c}_{IS}) < m + \bar{\gamma} + \bar{\mu}$ then E_1^* is locally asymptotically stable.*
3. *If $\bar{\beta} - \bar{c}_{IS} \leq 0$ then the basin of attraction of E_1^* includes $\mathbb{R}_+^2 - \{\mathbf{0}\}$.*

Proof: To prove the two first items it suffices to calculate the matrix of the linearization of system (7) at E_1^*

$$\begin{pmatrix} -(r - m) & \bar{a}r + \bar{\gamma} - S_1^*(\bar{c}_{SI} + \bar{\beta}) \\ 0 & S_1^*(\bar{\beta} - \bar{c}_{IS}) - (m + \bar{\gamma} + \bar{\mu}) \end{pmatrix}$$

One of the eigenvalues, $-(r - m)$, is negative while stability depends on the other one, $S_1^*(\bar{\beta} - \bar{c}_{IS}) - (m + \bar{\gamma} + \bar{\mu})$, being positive or negative: E_1^* is a saddle or (locally) asymptotically stable, respectively.

To prove the last assertion we first note that there exists no interior equilibria because the right-hand side of the I equation is always negative for positive S and I . Now the Poincaré-Bendixson theorem implies that there is no closed orbit in the interior of the positive quadrant and therefore that all positive solutions, that are forward bounded, must tend to the unique non-negative equilibrium point, E_1^* . ■

Up to now we have obtained the condition of non-extinction of the population, $r > m$, and a sufficient condition, $\bar{\beta} - \bar{c}_{IS} \leq 0$, for a disease-free scenario in the long term. This last condition says that if the competition coefficient \bar{c}_{IS} , representing the impact of susceptible on infected individuals, is larger than the transmission rate $\bar{\beta}$ then the infection disappears independently of the initial conditions. More significant cases exist when the simple competitive pressure of susceptible on infected individuals is not enough to compensate transmission.

From now on we are also assuming that $\bar{\beta} - \bar{c}_{IS} > 0$. In this case the conditions of local stability of the equilibrium E_1^* can be expressed in terms of the parameter

$$\bar{A} = \frac{m + \bar{\gamma} + \bar{\mu}}{\bar{\beta} - \bar{c}_{IS}}. \quad (9)$$

Thus, Proposition 3 can be restated as follows: for $r > m$ and $\bar{\beta} > \bar{c}_{IS}$, if $S_1^* > \bar{A}$ or $S_1^* < \bar{A}$ then the equilibrium E_1^* is a saddle point or locally asymptotically stable, respectively. The parameter \bar{A} represents a threshold population size allowing or not the increase of the infection when it is rare. If the susceptible population is close to its carrying capacity, S_1^* , a few infected individuals are able to spread the disease if the number of susceptible individuals is large enough, $S_1^* > \bar{A}$. On the other hand, the infection disappears if the susceptible population is under the threshold \bar{A} .

In the next results we search for conditions ensuring the endemicity of the infection. To express them in a simpler form we define another parameter

$$\bar{B} = \frac{\bar{a}r + \bar{\gamma}}{\bar{c}_{SI} + \bar{\beta}}, \quad (10)$$

that can be interpreted through the terms depending on I in the first equation of system (7). This equation can be written in the following form

$$\frac{dS}{dt} = (r - m)S - c_{SS}S^2 + (\bar{a}r + \bar{\gamma} - (\bar{c}_{SI} + \bar{\beta})S)I$$

where we note that depending on whether $\bar{a}r + \bar{\gamma} - (\bar{c}_{SI} + \bar{\beta})S(t)$ is positive or negative, the existence of infected individuals makes the susceptible growth rate increase or decrease, respectively. The size of the susceptible population determines if the infection has a positive or a negative effect on its growing. If $S(t) < \bar{B}$, the more infected individuals the larger the susceptible population growth rate, while $S(t) > \bar{B}$ yields a larger decrease of the susceptible population growth rate whenever there is a larger infected population.

Using parameters S_1^* , \bar{A} and \bar{B} the system (7) can be expressed as follows:

$$\begin{cases} \frac{dS}{dt} = c_{SS}S(S_1^* - S) + (\bar{c}_{SI} + \bar{\beta})(\bar{B} - S)I, \\ \frac{dI}{dt} = (\bar{\beta} - \bar{c}_{IS})(S - \bar{A})I - \bar{c}_{II}I^2. \end{cases} \quad (11)$$

The equation of the S -nullcline of the system (11), for $S_1^* \neq \bar{B}$, is

$$I = \Phi(S) = \frac{c_{SS}}{\bar{c}_{SI} + \bar{\beta}} \cdot \frac{S(S_1^* - S)}{S - \bar{B}}.$$

We are interested in the part included in the positive quadrant. This is for $S_1^* < \bar{B}$ an increasing branch going from the point $E_1^* = (S_1^*, 0)$ to the asymptote $S = \bar{B}$ (see Figure 1, left panel) and for $S_1^* > \bar{B}$ a decreasing branch going from the asymptote $S = \bar{B}$ to the point E_1^* (see Figure 1, right panel). In the case $S_1^* = \bar{B}$ the S -nullcline in the positive quadrant reduces to the line $S = \bar{B}$ (see Figure 1, center panel).

$$I = \Psi(S) = \frac{\bar{\beta} - \bar{c}_{IS}}{\bar{c}_{II}}(S - \bar{A})$$

It is immediate to prove that if $\bar{A} \geq \max\{S_1^*, \bar{B}\}$ there is no interior equilibria of the system (see panels in Figure 1) and thus, applying again the Poincaré-Bendixson theorem, we get that all positive solutions tend to E_1^* . We gather these results in the next proposition.

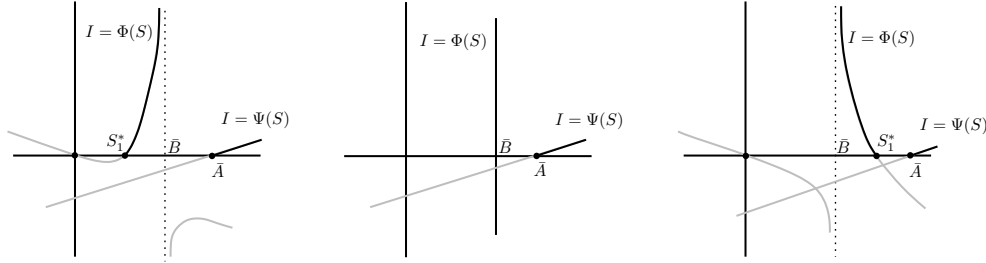


Figure 1: Possible profiles of the S -nullcline $I = \Phi(S)$ and the I -nullcline $I = \Psi(S)$ and the S -nullcline $I = \Phi(S)$ (in black, their intersection with the positive cone).

Proposition 4 *Let $r > m$ and $\bar{\beta} - \bar{c}_{IS} > 0$. If $\bar{A} \geq \max\{S_1^*, \bar{B}\}$ then the system (7) possesses a unique non-negative equilibrium point $E_1^* = (S_1^*, 0)$ that is asymptotically stable and attracts every positive solution.*

Condition $\bar{A} \geq \max\{S_1^*, \bar{B}\}$ tell us, on the one hand, that the infection cannot invade due to $\bar{A} \geq S_1^*$ and, on the other hand, that infected individuals cannot help in attaining the invasion threshold because $\bar{A} \geq \bar{B}$. The consequence is that infection disappears.

There are two situations for the infection to become endemic. The first one is allowing invasion, that is $S_1^* > \bar{A}$, that is treated in Proposition 5. The second one does not allow infection invasion for a low number of infected individuals, $S_1^* < \bar{A}$, but larger numbers of infected individuals might help the susceptible population growing, $\bar{A} \geq \bar{B}$, so as to maintain this latter over the invasion threshold. In Proposition 6 are detailed sufficient conditions to meet this second situation.

Proposition 5 *Let $r > m$ and $\bar{\beta} - \bar{c}_{IS} > 0$. If $S_1^* > \bar{A}$ then the system (7) possesses a unique interior equilibrium point $E_+^* = (S_+^*, I_+^*)$ that is locally asymptotically stable. If, in addition, $S_1^* < \bar{B}$, then E_+^* attracts every positive solution.*

Proof: The assumptions on parameters yield the existence of a unique interior equilibrium (see Figure 2). The asymptotic stability that follows can be proved by linearization.

Note that the condition $S_1^* > \bar{A}$ might not ensure that all positive solutions tends to the interior equilibrium. Due to the Poincaré-Bendixson theorem, it might happen that some of these solutions tend to a limit cycle included in the open positive quadrant surrounding the equilibrium.

Condition $S_1^* < \bar{B}$ excludes the existence of any limit cycle because the region $\mathcal{A} = \{(S, I); \Phi(S) \leq S \leq \Psi(S), 0 \leq I\}$ is an invariant ("trapping") subregion $\mathcal{A} \subset \mathbb{R}_+^2$ such that $E_+^* \in \partial\mathcal{A}$, the boundary of \mathcal{A} , and $\partial\mathcal{A} \cap \partial\mathbb{R}_+^2 \neq \emptyset$ (see Figure 2). That is, any orbit surrounding E_+^* must enter \mathcal{A} , but cannot leave from there. ■

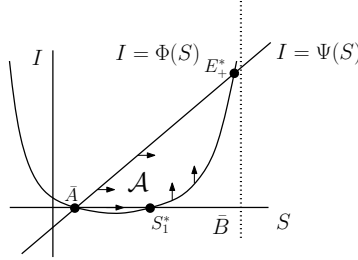


Figure 2: The invariant region $\mathcal{A} = \{(S, I); \Phi(S) \leq S \leq \Psi(S), 0 \leq I\}$ mentioned in the proof of proposition 5.

In any case, what condition $S_1^* > \bar{A}$ ensures is the endemicity of the infection. In the next Proposition 6 we state conditions leading the population to the disease-free state or toward conditional endemicity related with a bistable scenario. By conditional endemicity we mean that the outcome of the model can be either disease-free (see left panel in Figure 3) or with an endemic disease depending on the initial amount of susceptible and infected individuals; see the right panel in Figure 3.

Indeed, we introduce \mathcal{R} , that appears later in the corresponding proof, and drives the epidemic outcome. This quantity depends on the parameters of the model and allows to discriminate whether conditional disease endemicity is allowed or cannot occur.

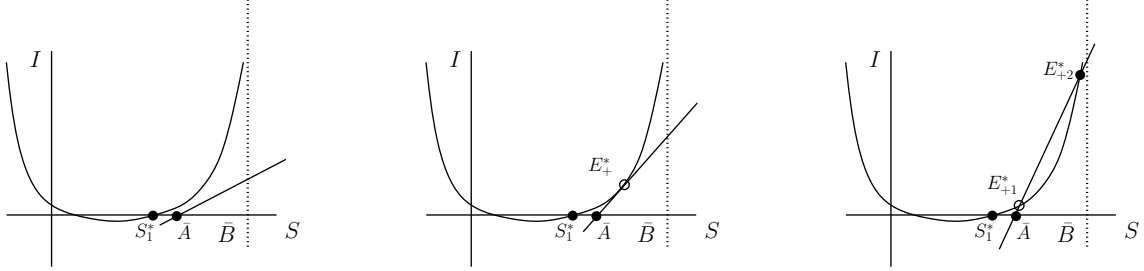


Figure 3: Related to Proposition 6, possible configurations of the nullclines when $S_1^* < \bar{A} < \bar{B}$. On the left panel S_1^* is global attractor. On the center panel S_1^* is an attractor. On the right panel the bistable case: S_1^* and E_{+2}^* are locally asymptotically stable while E_{+1}^* is a saddle.

Proposition 6 *Let $r > m$ and $\bar{\beta} - \bar{c}_{IS} > 0$. If $S_1^* < \bar{A} < \bar{B}$ then the system (γ) possesses the asymptotically stable equilibrium $E_1^* = (S_1^*, 0)$. Furthermore, let us define*

$$\mathcal{R} = \frac{\bar{c}_{II}(r - m) + (\bar{a}r + \bar{\gamma})(\bar{\beta} - \bar{c}_{IS}) + (\bar{c}_{SI} + \bar{\beta})(\bar{\mu} + \bar{\gamma})}{2\sqrt{(c_{SS}\bar{c}_{II} + (\bar{c}_{SI} + \bar{\beta})(\bar{\beta} - \bar{c}_{IS}))(\bar{a}r + \bar{\gamma})(\bar{\mu} + \bar{\gamma})}}.$$

We have:

1. if $\mathcal{R} < 1$ then there is no interior equilibrium point and the basin of attraction of E_1^* includes $\mathbb{R}_+^2 \setminus \{0\}$.
2. If $\mathcal{R} = 1$ then there is only one interior equilibrium point $E_+^* = (S_+^*, I_+^*)$ that is unstable. The equilibrium $E_1^* = (S_1^*, 0)$ attracts every solution with initial values in the interior of $\mathbb{R}_+^2 \setminus E_+^*$.
3. If $\mathcal{R} > 1$ then there are two interior equilibrium points $E_{+1}^* = (S_{+1}^*, I_{+1}^*)$ and $E_{+2}^* = (S_{+2}^*, I_{+2}^*)$, with $S_{+1}^* < S_{+2}^*$ and $I_{+1}^* < I_{+2}^*$. E_{+1}^* is a saddle and E_{+2}^* is locally asymptotically stable.

Proof: Note that the asymptotic stability of E_1^* follows directly from Proposition 3 since $S_1^* < \bar{A}$.

Next, we focus on showing the relation between \mathcal{R} and the existence of equilibrium points of system (7). Equating the nullclines $I = \Phi(S)$ and $I = \Psi(S)$ of system (7) yields

$$\frac{c_{SS}}{\bar{c}_{SI} + \bar{\beta}} \cdot \frac{S(S_1^* - S)}{S - \bar{B}} = \frac{\bar{\beta} - \bar{c}_{IS}}{\bar{c}_{II}}(S - \bar{A}).$$

Keeping in mind the definition of \bar{A} and \bar{B} , the previous expression is equivalent to

$$\begin{aligned}
0 = & (c_{ss}\bar{c}_{II} + (\bar{c}_{SI} + \bar{\beta})(\bar{\beta} - \bar{c}_{IS})) S^2 \\
& - (\bar{c}_{II}(r - m) + (\bar{a}r + \bar{\gamma})(\bar{\beta} - \bar{c}_{IS}) + (\bar{c}_{SI} + \bar{\beta})(\bar{\mu} + \bar{\gamma})) S \\
& + (\bar{a}r + \bar{\gamma})(\bar{\mu} + \bar{\gamma})
\end{aligned} \tag{12}$$

Now, direct calculations lead to the fact that \mathcal{R} being smaller than, equal to or larger than 1 is equivalent to the discriminant of equation (12) being negative, zero or positive. This yields the number of equilibrium points.

Note that when $\mathcal{R} < 1$ there is no interior equilibrium point and a direct application of the Poincaré-Bendixson theorem yields statement (1).

Concerning statement (2), direct calculations show that when $\mathcal{R} = 1$ the equilibrium E^* is not hyperbolic, so that we cannot use the linearization criterion. Note that the region $\mathcal{B} = \{(S, I); \Psi(S) \leq S \leq \Phi(S), 0 \leq I\}$ is an invariant region such that $E_+^* \in \partial\mathcal{B}$ and $\partial\mathcal{B} \cap \partial\mathbb{R}_+^2 \neq \emptyset$. Indeed, any solution with initial values in the interior of \mathcal{B} converges to E_0^* since $\Psi(S) < S < \Phi(S)$, which implies that E_+^* is unstable. The non existence of periodic orbits can be argued as done in the proof of Proposition 5.

We now assume $\mathcal{R} > 1$ and analyze the stability of the equilibria $E^* = (S^*, I^*)$ by means of the well known trace-determinant criterion. Let us consider the Jacobian matrix of the flow of system (7) at the equilibrium point which, taking into account that $\Phi(S^*) = I^* = \Psi(S^*)$, simplifies to

$$\mathcal{J} = \begin{pmatrix} -c_{SS}S^* - \frac{(\bar{a}r + \bar{\gamma})I^*}{S^*} & \bar{a}r + \bar{\gamma} - (\bar{C}_{SI} + \bar{\beta})S^* \\ (\bar{\beta} - \bar{c}_{IS})I^* & -\bar{c}_{II}I^* \end{pmatrix}.$$

This immediately yields $\text{tr}\mathcal{F} < 0$. Furthermore, a direct calculation leads to

$$\frac{\det\mathcal{J}}{I^*} = \frac{(c_{SS}\bar{c}_{II} + (\bar{C}_{SI} + \bar{\beta})(\bar{\beta} - \bar{c}_{IS})) (S^*)^2 + (\bar{a}r + \bar{\gamma}) (\bar{c}_{II}I^* - (\bar{\beta} - \bar{c}_{IS})S^*)}{S^*}$$

Using again the fact that $I^* = \Psi(S^*)$ if and only if $\bar{c}_{II}I^* = (\bar{\beta} - \bar{c}_{IS})S^* - (\bar{\mu} + \bar{\gamma})$, we have

$$\frac{\det\mathcal{J}}{I^*} = \frac{(k\bar{c}_{II} + (\bar{C}_{SI} + \bar{\beta})(\bar{\beta} - \bar{c}_{IS})) (S^*)^2 - (\bar{a}r + \bar{\gamma})(\bar{\mu} + \bar{\gamma})}{S^*},$$

so that $\det\mathcal{J} > 0$ is equivalent to

$$S^* > \sqrt{\frac{(\bar{a}r + \bar{\gamma})(\bar{\mu} + \bar{\gamma})}{k\bar{c}_{II} + (\bar{C}_{SI} + \bar{\beta})(\bar{\beta} - \bar{c}_{IS})}}, \tag{13}$$

which entails local stability. On the contrary, E^* is unstable if

$$S^* < \sqrt{\frac{(\bar{a}r + \bar{\gamma})(\bar{\mu} + \bar{\gamma})}{k\bar{c}_{II} + (\bar{C}_{SI} + \bar{\beta})(\bar{\beta} - \bar{c}_{IS})}}. \quad (14)$$

The S component of the equilibrium points E_{+1}^* and E_{+2}^* can be explicitly calculated from (12). Direct calculations show that S_{+1}^* fulfills condition (14) while condition (13) holds for S_{+2}^* . ■

4 Discussion

We have set up a model aimed to ascertaining the impact of an opportunistic disease outbreak in a population already affected by a primary disease by assuming that both diseases evolve within different time scales. For the discussion of results, let us remind the two main aims stated in the introduction. On the one hand, we wanted to know whether the coinfection by a secondary disease produces epidemiological scenarios not allowed by the primary disease submodel or not. In the latter case, it is of interest to determine if coinfection has any influence on the actual outcome of the model, even if just among those allowed by the primary disease submodel.

The answer to the first question is negative, as we have pointed out at the end of section 2. Thus, the catalog of possible qualitative epidemic behaviors remains unchanged by the influence of a secondary disease under the assumptions considered here. We can restate this fact by saying that there is neither functional nor dynamical emergence [3].

Nevertheless, the effect of the the opportunistic disease must be taken into account. In Section 3 we have found that \bar{A} , \bar{B} , S_1^* , as well as \mathcal{R} are key parameters to describe the outcome of the model. All of them, but S_1^* , depend on ν^* , the fraction of coinfecting individuals which, in turn, depends on λ/δ , the ratio of the parameters describing the opportunistic disease dynamics. It means that the opportunistic disease can be decisive in the long-term behavior of the slow-fast model. Therefore, the interest lies on how \bar{A} , \bar{B} and \mathcal{R} vary with the quotient δ/λ . Unfortunately, such a dependence is, in general, not simple (just see equations (5) and (8)) and we resort to numerical tools to illustrate the effect of varying δ/λ in the outcome of the model. Figure 4 displays the different outcomes of the aggregated model as function of δ and λ : In yellow: values of δ and λ leading to the disease-free scenario. In orange: values leading to an endemic primary infection outcome. In gray: conditional coinfection, meaning

values leading to either disease-free or endemic coinfection scenario, depending on the the initial amount of susceptible and infected individuals. In red: values leading to disease endemic coinfection outcome.

In the right picture of Figure 4, the epidemiological outcome changes from disease-free to endemic coinfection as the ratio δ/λ increases and crosses the threshold $\delta/\lambda = 1$. Instead, in the left picture of Figure 4, note that the disease-free region (in the parameters space) overlaps the region $\lambda > \delta$ (above the dotted line) where the opportunistic disease would be able to invade if there were primary infected in the population. As the ratio δ/λ increases, the epidemiological outcome changes from disease-free to conditional coinfection and a further increase leads to endemic coinfection. The only difference between the parameter values used in each figure is on c_{SS} and β_V . And this fact leads us to another interesting finding: there is a delicate interplay between competition coefficients and infection parameters, captured by the definition of \bar{A} , \bar{B} , S_1^* and \mathcal{R} , which must be taken into account. Although we could not derive general results of such an interdependence, we have shown that it must be taken into account.

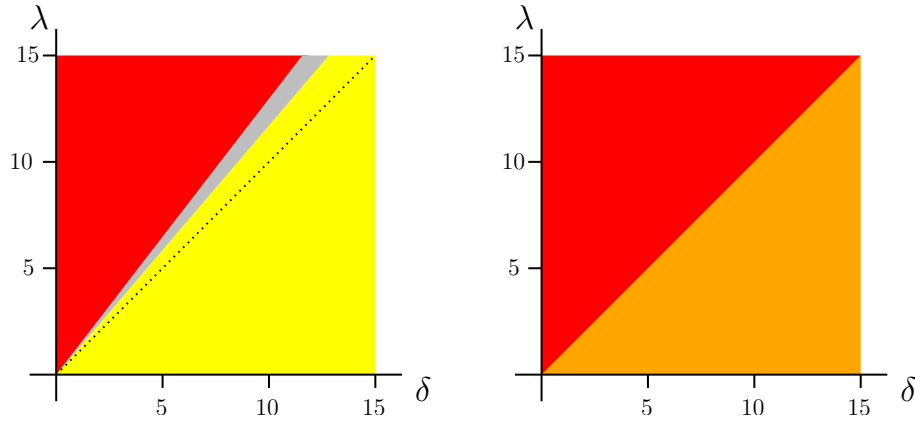


Figure 4: Possible epidemic outcomes. Yellow: disease-free. Orange: endemic primary infection. Gray: disease-free or endemic coinfection, depending on initial values. Red: endemic coinfection. Left figure parameter values: $a_U = 0.9$, $a_V = 0.7$, $r = 26$, $m = 12$, $\mu_U = 0.3$, $\mu_V = 0.5$, $c_{SS} = 3.8$, $c_{SU} = 0.5$, $c_{SV} = 0.5$, $c_{US} = 2.6$, $c_{UU} = 0.1$, $c_{UV} = 1$, $c_{VS} = 0.5$, $c_{VU} = 4$, $c_{VV} = 4$, $\beta_U = 4$, $\beta_V = 8$, $\gamma = 0.2$. The parameter values in the right figure are the same as before but $m = 17$, $c_{SS} = 2.8$, $\beta_V = 4$.

Summing up, both the irruption of an opportunistic disease and the competitive pressure of individuals being in different epidemiological state may affect the evolution of the primary disease outbreak. The effect can be determined by means of the param-

eters \bar{A} , \bar{B} and \mathcal{R} on δ/λ . An it leads us to the second objective of this work.

Related to our second objective, our results point out two different kinds of mechanisms to modulate the outcome of the model, each of them feasible within certain ranges of the parameter values.

On the one hand, having control on parameters δ and λ may allow certain leeway to reverse/promote epidemic outbreaks or infection/coinfection scenarios. Indeed, once the actual parameter values of the model are known one can compute (the equivalent of) Figure 4 and get enhanced comprehension on the epidemiological context as well as ascertaining the effect on the epidemic outbreak of changes on δ or λ . In this sense, it is interesting to note that any action or measure taken to modify the secondary infection recovery rate δ or transmission rate λ such that δ/λ remains constant is completely ineffective. In addition, controlling individuals competitive pressure may be relevant for the epidemiological outcome.

On the other hand, the results in propositions 3 and 6 suggest that acting on the susceptible/infected individuals population size in order to keep the population above/below certain threshold allows to have control on epidemic outbreaks. In particular, according to Proposition 3, \bar{A} is a susceptible population size threshold allowing or not the increase of the infection when it is rare. Therefore, introducing/culling (removing) susceptible individuals to bring the population above/below this threshold may certainly modify the outcome. Besides, under the hypotheses of Proposition 6, we show that when $\mathcal{R} > 1$ whether the disease establishes itself or not depends on the initial amount of susceptible and infected individuals. From a mathematical point of view, this scenario is characterized by the fact that the disease-free equilibrium E_1^* and an endemic disease (interior) equilibrium E_{+2}^* coexist and are locally asymptotically stable. There is also a saddle node interior equilibrium E_{+1}^* . The stable manifold of E_{+1}^* separates the basins of attraction of the disease-free and the endemic disease steady states. This stable manifold cannot be calculated straightforward, but can be computed using, for instance, the results in [10] and [11].

A final comment has to do with the selection of the transmission form of the opportunistic disease. Preliminary calculations show that considering DDT instead of FDT leads to equivalent results. This means that even if the nullclines are different, the possible outcomes (say the dynamical scenarios) of the corresponding aggregated model are the same.

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References

- [1] Abu-Raddad L, Patnaik P, Kublin J (2006). Dual Infection with HIV and Malaria Fuels the Spread of Both Diseases in sub-Saharan Africa. *Science* 314: 1603–1606.
- [2] Alcabes P, Schoenbaum E, Klein R (1993). Correlates of the Rates of Decline of CD4+ Lymphocytes among Injection Drug Users Infected with Human Immunodeficiency Virus. *Am J Epidemiol* 137:989–1000.
- [3] Auger P, Bravo de la Parra R, Poggiale JC, Sánchez E, Nguyen Huu T (2008). Aggregation of variables and applications to population dynamics. In: P. Magal, S. Ruan (Eds.), *Structured Population Models in Biology and Epidemiology*, Lecture Notes in Mathematics, vol. 1936, Math Biosci Subseries. Springer, Berlin, pp. 209–263.
- [4] Auger P, Poggiale JC, Sánchez E (2012). A review on spatial aggregation methods involving several time scales. *Ecol Complex* 10:12–25.
- [5] Baron S (Ed.) (1996). *Medical Microbiology* 4th Edition. The University of Texas Medical Branch at Galveston.
- [6] Bedhomme S, Agnew P, Sidobre C, Michalakakis Y (2005). Prevalence-dependent costs of parasite virulence. *PLoS Biol.* 3, e262.
- [7] Begon M, Bennett M, Bowers RG, French NP, Hazel SM, Turner J (2002). A clarification of transmission terms in host-microparasite models: numbers, densities and areas. *Epidemiol Infect* 129:147–153.
- [8] Brauer F, Castillo-Chávez C (2001). *Mathematical Models in Population Biology and Epidemiology*. Springer, New York.
- [9] Brauer F (2008). Compartmental Models in Epidemiology. In: F. Brauer, P. van den Driessche J. Wu (Eds.), *Mathematical Epidemiology*, Lecture Notes in Mathematics, vol. 1945, Math Biosci Subseries. Springer, Berlin, pp. 19–79.
- [10] Cavoretto R, Chaudhuri S, De Rossi A, Menduni E, Moretti F, Rodi MC, Venturino E (2011). Approximation of dynamical system’s separatrix curves, *Numerical Analysis and Applied Mathematics ICNAAM 2011*, T. Simos, G. Psihoyios, Ch. Tsitouras, Z. Anastassi (Editors), AIP Conf. Proc. 1389, 1220–1223; doi: 10.1063/1.3637836.

- [11] Cavoretto R, De Rossi A, Perracchione E, Venturino E. Reliable approximation of separatrix manifolds in competition models with safety niches, to appear in *International Journal of Computer Mathematics*.
- [12] Cox FE (2001). Concomitant infections, parasites and immune responses. *Parasitol.* 122. Suppl: S23–38.
- [13] Eaton DK, Lowry R, Brener ND, Kann L, Romero L, Wechsler H (2011). Trends in Human Immunodeficiency Virus and Sexually Transmitted Disease Related Risk Behaviors Among U.S. High School Students, 1991–2009. *Am J Prev Med* 40(4):427–433.
- [14] Ensoli F, Sirianni MC (2002). HIV/HCV Co-Infection: Clinical and Therapeutic Challenges. *A.I.D.S.* 16(10): 1419–1420.
- [15] Griffiths EC, Pedersen ABP, Fenton A, Petchey OP (2011). The nature and consequences of coinfection in humans. *J Infect* 63 (3): 200–206.
- [16] Ivan E, Crowther NJ, Mutimura E, Osuwat LO, Janssen S, Grobusch MP (2013). Helminthic Infections Rates and Malaria in HIV-Infected Pregnant Women on Anti-Retroviral Therapy in Rwanda. *PLoS Neglected Tropical Diseases* 7(8): doi:10.1371/journal.pntd.0002380.
- [17] Herring DA, Sattenspiel L (2007). Social contexts, syndemics, and infectious disease in northern Aboriginal populations. *Am J Hum Bio* 19(2):190–202.
- [18] Kang Y, Castillo-Chávez C (2014). Dynamics of SI models with both horizontal and vertical transmissions as well as Allee effects. *Math Biosci* 248:97–116.
- [19] Koster FT, Curlin GC, Aziz KM, and Haque A (1981). Synergistic impact of measles and diarrhoea on nutrition and mortality in Bangladesh. *Bull World Health Organ.* 59(6): 901–908.
- [20] Kwan C, Ernst J (2011). HIV and Tuberculosis: A Deadly Human Syndemic. *Clin Microbiol Rev* 24(2):351–376.
- [21] Marvá M, Poggiale JC, Bravo de la Parra R (2012). Approximate aggregation of a two time scales periodic multi-strain sis epidemic model: a patchy environment with fast migrations. *Ecol Complex.* 10(1):34–41 2012
- [22] McCallum H, Barlow N, Hone J (2001). How should pathogen transmission be modeled?. *Trends Ecol Evol* 16(6):295–300.

- [23] Merrill S (2009). *Introducing Syndemics: A Critical Systems Approach to Public and Community Health*. Wiley.
- [24] Sieber M, Malchow H, Hilker FM (2014) Disease-induced modification of prey competition in eco-epidemiological models. *Ecol Complex* 18:74-82.
- [25] Singer M and Clair S (2003). Syndemics and Public Health: Reconceptualizing Disease in Bio-Social Context. *Medical Anthropology Quarterly, New Series*, Vol. 17, No. 4 pp. 423–441.
- [26] Symmers WS (1965). Opportunistic Infections. The Concept of 'Opportunistic Infections'. *Proc R Soc Med* 58:341–346.
- [27] World Health Organization. WHO Report 2011: Global Tuberculosis Control. 2011
- [28] Zlamy M et al. (2013) The impact of Rotavirus mass vaccination on hospitalization rates, nosocomial Rotavirus gastroenteritis and secondary blood stream infections *BMC infectious diseases* Vol: 13, 112